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Consensus statement from European experts on the diagnosis, management, and treatment of multiple myeloma: from standard therapy to novel approaches

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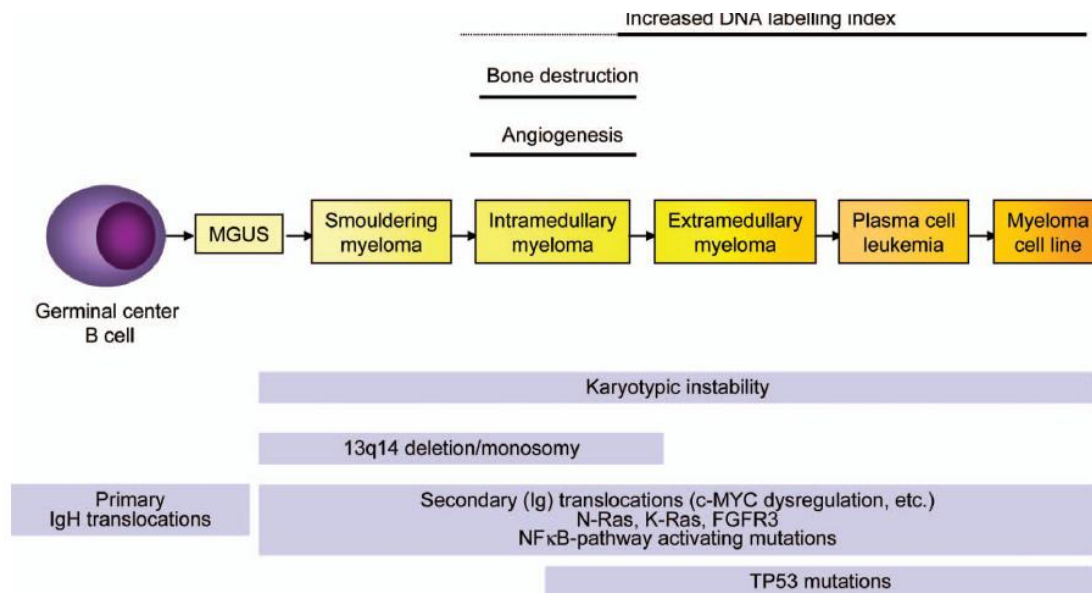
ABSTRACT

Treatment for multiple myeloma (MM) has changed beyond recognition over the past two decades. During the early 1980s, MM inevitably resulted in a slow progressive decline in quality of life until death after about 2 years, while today patients can expect a 50% chance of achieving a complete remission, median survival of 5 years, and a 20% chance of surviving longer than 10 years. An international expert opinion meeting (including members of the GIMEMA and DSMM study groups) was held in 2009. One of the outcomes of the meeting was the development of a consensus statement outlining contemporary optimal clinical practice for the treatment of MM. The international panel recommended that the state of the art therapy for MM should comprise: (a) evidence-based supportive care, (b) effective and well-tolerated chemotherapeutic regimens, (c) autologous hematopoietic stem cell transplant (ASCT) for patients suitable for intensive conditioning therapy, and (d) evidence-based incorporation of novel anti-MM agents. Maintenance strategies have also become increasingly important for the prolongation of remission after front-line therapies. In addition, improved understanding of the biology of MM has led to the development of novel biological therapeutic agents such as thalidomide, lenalidomide, bortezomib, and others. These agents specifically target intracellular mechanisms and interactions, such as those within the bone marrow microenvironment, and have been integrated into MM treatment. This report reviews recent clinical advances in the treatment strategies available for MM and provides an overview of the state of the art management of patients with MM.

Introduction

Multiple myeloma (MM) is a mature B-cell-lymphoid neoplasm and accounts for approximately 10% of all hematologic neoplasias [1,2]. It is characterized by the monoclonal proliferation and accumulation of plasma cells (PCs) in the bone marrow (BM) and an excess of secreted monoclonal immunoglobulins (paraprotein or M-band) [1–3]. MM is thought to be invariably preceded by a premalignant phase, monoclonal gammopathy of undetermined significance (MGUS) [4], which is present in more than 3% of the general population above the age of 50 years and progresses to MM at a rate of 1% per year (Figure 1). The annual incidence of MM is 4.3 per 100 000, with a higher prevalence of both MM and MGUS in Western countries. In general, these plasma cell dyscrasias affect males slightly more frequently than females, and are twice as common in blacks than in whites. The median age of patients with MM at diagnosis is 69 years for men and 72 years for women. The etiology of MM is largely unknown; however, familial/genetic predisposition, radiation, benzene, other organic solvents, herbicides, and insecticides are considered by some to play a role [1–3, 5–7].

Figure 1. Clinical evolution and molecular pathogenesis of MM (figure modified according to illustrations of Sirohi *et al.*, 2004 [184] and Harousseau *et al.*, 2009 [185]), illustrating the disease evolution from MGUS to smoldering-, intramedullary-, and extramedullary myeloma and eventually plasma cell leukemia, correlating with defined molecular events as depicted. MGUS, monoclonal gammopathy of undetermined significance; NFκB, nuclear factor κB; Ig, immunoglobulin.



In the majority of patients a paraprotein is detectable in the blood serum and/or urine. More advanced stages of MM typically present with skeletal destruction manifesting as osteolytic lesions, osteopenia, and/or pathologic fractures. Other common clinical features include renal insufficiency, hypercalcemia, myelosuppression with anemia, bleeding, immunodeficiency, and hyperviscosity. The Mayo Clinic and International Myeloma Working Group (IMWG) have developed simplified criteria for the diagnosis of symptomatic MM, whereby the following three criteria must be met: (1) the presence of a paraprotein in the serum and/or urine, (2) the presence of at least 10% clonal bone marrow plasma cells, and (3) the presence of related organ or tissue impairment (ROTI), for example hypercalcemia, renal impairment, anemia, and/or bone disease (CRAB).

The clinical staging system previously proposed by Durie and Salmon is based on factors correlating with tumor mass [1–3,8], and has largely been replaced by the International Staging System (ISS) [9]. Besides disease stage, other important prognostic factors that define patients as high-risk or standard-risk include: deletion of chromosome 13 or hypodiploidy on conventional karyotyping; deletion of chromosome 17p-, t(4;14), or t(14;16) on interphase karyotypic analysis (fluorescence *in situ* hybridization, FISH); and a plasma labeling index of $\geq 3\%$ [10]. The presence of any one of these risk factors identifies an individual patient as having high-risk MM, where the median overall survival (OS), even with tandem stem cell transplant (SCT), is only 2–3 years, as opposed to 5 or more years for those patients with MM with standard-risk disease [10]. Overall the median OS is 3–5 years, and the main goals of treatment are the achievement of higher and more prolonged complete remission (CR) rates that translate into better long-term OS and improved quality of life with fewer MM-associated symptoms [1,11].

In randomized trials, high-dose chemotherapy and autologous hematopoietic stem cell transplant (ASCT) produces an OS advantage compared to conventional chemotherapy [12–15], and patients with high-risk MM, when eligible, are now routinely offered combination induction therapies incorporating new agents followed by ASCT. Subsequent strategies including reduced intensity conditioning (RIC)-allogeneic (allo)-SCT in selected patients [10,16,17] and/or the use of

maintenance therapy after ASCT are now being increasingly incorporated into the treatment paradigm. Allo-SCT is thought to be potentially curative; however, while long-term results are still awaited it is clearly evident that the introduction of RIC-regimens has decreased treatment related morbidity and mortality (TRM) considerably when compared to previously utilized myeloablative conditioning approaches [16,17]. The introduction of (a) earlier ASCTs; (b) tandem transplants within clinical trials; and (c) novel anti-MM drugs as part of primary upfront therapy and/or maintenance therapy is hoped to further improve the outcome of MM in the near future. These more intensive treatment strategies can also be contemplated in selected older patients with increasing success. This can be attributed to advances in reduced intensity induction regimens and, in particular, improved supportive care and more informative comorbidity assessment strategies [1,11,18,19].

Novel anti-MM drugs have also expanded therapeutic prospects, and current trials are evaluating a range of innovative agents including immunomodulatory drugs (IMiDs, e.g. pomalidomide), proteasome inhibitors (S-2209, NPI-0052), multikinase inhibitors, farnesyl transferase inhibitors, histone deacetylase (HDAC) inhibitors (Vorinostat, KD7150, MS-275, Tubacin, LBH589 [Panobinostat®]), heat shock protein-90 (HSP-90) inhibitors (NVP-AUY922), various monoclonal antibodies, and PI-3K/PKD/mTOR (phosphatidylinositol 3-kinase/protein kinase D/mammalian target of rapamycin) inhibitors (NVP-BEZ235) that aim to further improve the outcome for patients with MM.

Design and methods

One of the principal challenges faced today in the management of MM is how to best exploit diagnostic information so as to best inform prognosis and the selection of therapies, thus better defining the optimal use of new anti-MM agents and their various combinations in the different stages of the disease. Furthermore, as the management of MM is rapidly changing, guidelines that incorporate strategies for the optimal management of the disease are becoming increasingly important and help us to employ the best available treatments for patients with MM. Guidelines currently available include those from the National Comprehensive Cancer Network [20], UK Myeloma Forum, Nordic Myeloma Study Group, and the International Myeloma Foundation, recommendations based on expert opinion meetings [21], and various hematology groups (e.g. Deutsche Gesellschaft für Hämatologie und Onkologie [DHGO]; www.dgho.de/cms.php?id=705) [22–25].

An international expert opinion meeting was held in Stresa, Italy, from 17 to 19 May 2009, which brought together members of the German (Deutsche Studiengruppe Multiples Myelom, DSMM) and Italian (Gruppo Italiano Malattie Ematologiche dell'Adulto, GIMEMA) MM study groups and an international faculty with extensive clinical and scientific experience in MM. Different consensus panels coordinated by two chairmen defined several areas for MM-specific recommendations: (1) front-line therapy for young patients (Einsele, Cavo); (2) front-line therapy for elderly patients (Palumbo, Straka, Knop); (3) treatment of relapsed and refractory patients (Boccardo, Kropff); (4) the use of novel agents (Morabito, Gramatzki, Spencer); (5) the role of allogeneic stem cell transplant (Bruno, Bunjes); (6) guidelines and management of side effects (Engelhardt, Patriarca, Polliack); and (7) bone disease, biobanking, cytogenetics, and molecular studies (Sezer, Hajek, Omede, Neri). These experts reviewed published literature and then expressed their recommendations based on scientific evidence and clinical practice experience. The expert panels, where applicable, based recommendations on the results of at least one large prospective randomized trial. If evidence from phase 3 studies was unavailable in a specific area, the expert panel expressed suggestions based on the results of prospective non-randomized studies, clearly indicating the need for further data. Thus, these recommendations reflect expert opinion,

with the summaries provided here illustrating how scientific results are perceived by medical practitioners and how they are subsequently applied in daily clinical practice.

To treat or not to treat: clinical considerations for initiation of therapy including diagnostics

Criteria that differentiate MGUS, asymptomatic (smoldering) MM, symptomatic (including non-secretory) MM, solitary plasmacytoma, and extramedullary (EM) MM have been defined by the IMWG [8]. MGUS is defined by the presence of a paraprotein <30 g/L, BM clonal plasma cells <10%, but no evidence of MM, other B-cell proliferative disorders, or light-chain (AL) amyloidosis. In smoldering MM the paraprotein is ≥ 30 g/L and/or clonal BM plasma cells are $\geq 10\%$, without related organ or tissue impairment (ROTI). MM exhibits some or all of the pathologic findings as described above, as well as ROTI. Non-secretory MM is characterized by the absence of a paraprotein in the serum and urine, but displays BM plasmacytosis and ROTI. To precisely differentiate these distinct entities, the investigations outlined in Table I are required, and thereby facilitate appropriately timed therapeutic intervention.

Table I. Diagnostic criteria for MGUS, smoldering or indolent multiple myeloma (MM), and symptomatic MM.

MGUS	Smoldering or indolent MM	Symptomatic MM [†]
Serum M-protein > 30 g/L or	Serum M-protein > 30 g/L or	Monoclonal plasma cells (bone marrow) $\geq 10\%$ or biopsy proven plasmacytoma
Bone marrow clonal plasma cells < 10%	Bone marrow clonal plasma cells > 10%	Monoclonal protein in serum and/or urine [‡]
No evidence of myeloma-related end-organ damage:	No evidence of myeloma-related end-organ damage or tissue impairment (bone lesions*) or symptoms	Evidence of myeloma-related end-organ damage (≥ 1):
Normal serum calcium, hemoglobin level and serum creatinine		C, calcium (serum > 2.75 mmol/L)
No bone lesions		R, renal insufficiency (crea > 2 mg/dL)
No evidence of amyloidosis or light chain deposition disease		A, anemia (hemoglobin < 10 g/dL)
		B, lytic bone lesions or osteoporosis

*On skeletal X-ray survey and/or other imaging.

[†]Including stage IB, II, and IIIA/B myeloma by Durie-Salmon.

[‡]Non-secretory disease: $\geq 30\%$ monoclonal bone marrow plasma cells and/or biopsy proven plasmacytoma. MGUS, monoclonal gammopathy of undetermined significance; crea, creatinine.

The requirement for a simplified prognostic scoring system has been met by the introduction of the International Staging System (ISS) as devised by Greipp *et al.* [9] that incorporates serum albumin and β_2 -microglobulin at the time of diagnosis. Furthermore, advances in both metaphase cytogenetics and FISH on interphase cells have improved the ability to detect prognostically relevant chromosomal abnormalities. FISH-based abnormalities including 17p deletion, t(4;14), and t(14;16) and the detection with metaphase cytogenetics of del13 or hypoploidy all confer a worse prognosis, and, although less readily available, a plasma cell labeling index (PCLI) >3% similarly correlates with a poor outcome. These prognostic factors, and potentially other novel predictive markers currently being assessed, help to define different prognostic groups of MM patients, may identify novel targets for specific anti-MM treatment strategies, and also facilitate the stratification of patients for innovative treatment strategies and clinical trials [18,19,26,27]. Optimizing response via the attainment of a CR (complete response) and its valid recognition are important goals of contemporary MM therapy. CR is currently defined according to European

Group for Blood and Marrow Transplantation (EBMT) or IMWG criteria, but can be more stringently defined by the incorporation of multiparameter flow cytometry (MFC), thus allowing for the more accurate assessment of ‘minimal residual disease’ (MRD). MRD assessment is standard in many hematologic malignancies, but is still considered investigational in MM. Prospective analyses of the prognostic importance of MRD detection by MFC in patients with newly diagnosed MM uniformly treated with ASCT have been shown to be of importance, since progression-free survival (PFS) and OS were longer in patients who were MRD-negative versus MRD-positive at day 100 after ASCT. Furthermore, multivariate analysis identified MRD status by MFC at day 100 after ASCT as the most important independent prognostic factor for PFS and OS, illustrating the clinical impact of MRD detection and therefore the need for further refinement of MM response criteria incorporating MRD analyses [28].

A report from the European Myeloma Network (EMN) outlined technical MFC recommendations, including: (1) CD38, CD138, and CD45 should all be included in at least one tube for PC identification and enumeration; the primary gate should be based on CD38 vs. CD138 expression; (2) after treatment, clonality assessment is only likely to be informative when combined with immunophenotypic findings to detect abnormal cells, and MFC should be used for demonstrating a stringent CR; (3) for detection of abnormal PCs a minimal panel should also include CD19 and CD56, but a preferred panel would also include CD20, CD117, CD28, and CD27; (4) discrepancies between the percentage of PCs detected by MFC and light microscopy and cytology are primarily related to sample quality; therefore, it is important to determine that marrow elements are present in follow-up samples, particularly normal PCs in the MRD-negative cases [29].

Induction therapy for young patients

Induction therapy prior to ASCT is aimed at achieving de-bulking of disease and symptom control, and facilitates the collection of peripheral blood stem cells (PBSCs). However, the prolonged use of alkylating agents, dense BM infiltration, prior irradiation, advanced age, and elevated plasma viscosity are all factors which may impair stem cell procurement and subsequent engraftment [30–32]. Therefore, if ASCT is contemplated, prolonged alkylating agent exposure should be avoided [30]. Furthermore, the prolonged use of alkylating agents prior to PBSC collection also increases the risk of myelodysplasia (MDS) post-transplant.

VAD (vincristine, doxorubicin, dexamethasone) chemotherapy has been used as an induction regimen for many years; however, PBSC mobilization may be better facilitated by alternative regimens, such as IEV (ifosfamide, etoposide, epirubicin), CEV (cyclophosphamide, etoposide, epirubicin), or cyclophosphamide alone [30,33]. Furthermore, while objective response rates achieved with VAD are in the range of 40–70%, its administration is demanding, principally because infusional adriamycin and vincristine require a central line, with the associated risk of infective and thrombotic complications. Response rates with dexamethasone alone [34] are in the order of 40–50%, and associated with less treatment-related toxicity. These factors and the introduction of several newer induction regimens mean that VAD is no longer recommended as induction therapy.

Several newer induction regimens currently that are suitable prior to ASCT include bortezomib-based regimens (e.g. VCD [bortezomib, cyclophosphamide, dexamethasone] [35], VTD [bortezomib, thalidomide, dexamethasone], or PAD [bortezomib, adriamycin, dexamethasone]) [21,24,36], thalidomide/dexamethasone (Thal/Dex) [36,37], or lenalidomide/dexamethasone (Rev/Dex [given as RD or Rd]; e.g. four cycles of Rd before cyclophosphamide mobilization and melphalan 200 (MEL200) [38]); (Table II) the latter eventually may be combined with cyclophosphamide. However, the potential detrimental impact of lenalidomide on subsequent PBSC collection requires clarification in appropriately designed clinical trials.

Table II. First-line treatment in newly diagnosed multiple myeloma (phase III studies).

Reference	No. of patients	CTx	Overall response rate (%)	Median PFS (months)	Median TTP (months)	Median OS (months)
[163]	289	TD vs. MP	68 vs. 50	16.7 vs. 20.7	21.2 vs. 29.1	41.5 vs. 49.4
[164]	198	RD vs. D	79.2 vs. 26.2	77 vs. 55% at 1 year	NA	93 vs. 91% at 1 year
[165]	445	RD vs. Rd	82 vs. 70	NA	NA	87 vs. 75% at 2 years
[119,166]	255	MPT vs. MP	76 vs. 47.6	21.8 vs. 14.5	NA	45.0 vs. 47.6
[15]	321	MPT vs. MP	76 vs. 35	27.5 vs. 17.8	NA	51.6 vs. 33.2
[167]	362	MPT vs. MP	57 vs. 38	15 vs. 14	NA	30 vs. 30
[119]	344	MPT vs. MP	66 vs. 47	14 vs. 10	NA	37 vs. 30
[168]	357	MPT vs. MP	42 vs. 28	16 vs. 14	20 vs. 18	29 vs. 33
[118]	232	MPT vs. MP	62 vs. 31	24.1 vs. 19	NA	45.3 vs. 27.6
[123]	682	VMP vs. MP	71 vs. 35	NA	24 vs. 17	87 vs. 78% at 16 months
[169]	246	VMP vs. VPT	78 vs. 78	NA	NA	NA
[170]	393	VMPT vs. VMP	55 vs. 42	83.9 vs. 75.7% at 2 years	NA	89.5 vs. 88.7% at 3 years

CTx, chemotherapy; TD: thalidomide plus high-dose dexamethasone; MP, melphalan plus prednisone; RD, lenalidomide plus high-dose dexamethasone; D, dexamethasone; Rd, lenalidomide plus low-dose dexamethasone; MPT, MP plus thalidomide; VMP, MP plus bortezomib; VPT, bortezomib, prednisone, thalidomide; VMPT, VMP plus thalidomide; PFS, progression-free survival; TTP, time to progression; OS, overall survival; NA, not applicable.

Thalidomide and thalidomide analogs



Initially given in relapsed MM as a single agent, thalidomide has been shown to induce overall response rates (ORRs) of approximately 30% [39]; however, when combined with dexamethasone and/or alkylators, increased response rates are seen [40]. As thalidomide and its analogs are more effective with earlier treatment initiation, they have been included in a variety of induction schedules with substantially lower thalidomide doses (100–200 mg/day), thereby minimizing toxicity [40–42]. It is possible that this dose may be able to be lowered even further in newer combination strategies [40–44]. The OPTIMUM study compared the tolerability and efficacy of high-dose dexamethasone (Dex) versus 100, 200, or 400 mg of thalidomide for up to 12 cycles in 499 patients with relapsed/refractory MM, and demonstrated an improved time to progression (TTP) and response duration with all three thalidomide doses when compared to high-dose dexamethasone [45,46].

Thal/Dex was used in an Eastern Cooperative Oncology Group (ECOG) randomized trial of 202 patients, where the best response with four cycles of treatment was significantly higher with Thal/Dex when compared to dexamethasone alone (63% vs. 41%, respectively; $p=0.002$).

Unfortunately, survival was not planned as an end-point for the study, and the analysis was not powered to compare differences in survival between both arms. Preliminary results from a separate randomized, double blind, placebo-controlled study comparing Thal/Dex with dexamethasone alone as primary treatment in 470 patients also confirmed these results [47]. These data led to the accelerated Food and Drug Administration (FDA) approval of Thal/Dex for newly diagnosed MM. Of additional interest is a case–control study that compared the efficacy and toxicity of Rev/Dex versus Thal/Dex in 411 patients with newly diagnosed MM, suggesting that the former is well tolerated and more effective as initial therapy, but this needs to be confirmed in randomized trials [48].

Rev/Dex has been tested in a phase 2 trial at the Mayo Clinic, and has shown impressive responses in patients with newly diagnosed MM [49]. The ECOG has also reported on a randomized trial with Rev/high-dose dexamethasone (RD: 40 mg days 1–4, 9–12, 17–20; 480 mg of dexamethasone per 28 day cycle) versus Rev/low-dose dexamethasone (Rd: 160 mg of dexamethasone per 28 day cycle) showing a better short-term OS and lower toxicity with Rd [50].

Bortezomib-based regimens have demonstrated high response rates, which are between 70 and 80% with bortezomib plus dexamethasone; bortezomib, thalidomide, dexamethasone (VTD); or other bortezomib-based combinations (e.g. VMPT [bortezomib, melphalan, prednisone, thalidomide]; [51,52] (Table II)).

Transplants and conditioning

Current guidelines from Europe and the USA recommend that high-dose therapy and ASCT should be part of the initial therapy in younger patients with newly diagnosed MM with an adequate performance status [53]. As the biological age may differ from the chronological age, it is important to take associated comorbidities into account when determining whether a patient is a candidate for ASCT [18,19,26]; therefore, a strict age cut-off regarding ASCT is not always appropriate. While an upper age limit of 65–70 years is today's practice in Europe, in study protocols, patients up to the age of 75 years have been treated with age-adapted high-dose melphalan: melphalan 200 mg/m²

(MEL200) is recommended for patients <65 years of age, whereas for fit elderly patients, doses of 140 mg/m² or 100 mg/m² may be considered. For patients >75 years of age and/or with significant comorbidities, consideration should be given to reducing the dose of any given therapy. Although allo-SCT may be a potentially curative strategy [3,16,17], cure in MM still remains rare. Furthermore, the improvements in outcome seen over the past decade are almost certainly the culmination of a range of factors, including better patient selection for clinical trials and the administration of new treatment options, such as targeted conditioning therapies, the inclusion of novel agents into induction therapy, more intensive, yet non-myeloablative conditioning regimens, the use of tandem transplants, peripheral blood cells, graft engineering, post-transplant maintenance approaches, the adoption of specific and non-specific immunotherapies, and risk-adapted approaches for defined genetic abnormalities [54]. In this respect it is noteworthy that to date, del(17p13) remains a negative prognostic factor, whereas the adverse impact of t(4;14) might be overcome with allo-SCT [55].

Since it is safe and effective, ASCT as opposed to allo-SCT has become the standard of care in MM, with only 6% of transplant-eligible patients undergoing an allo-SCT while 94% receive an ASCT, thereby making MM the most common indication for ASCT worldwide [56]. Randomized trials have shown that ASCT is superior to conventional chemotherapy, resulting in an improved CR rate (22–44% vs. 5–8%) and a 12–30-month prolongation of event-free survival (EFS) and OS [12–15 ,54] (Table III).

Table III. Novel agent combinations with autologous stem cell transplant (ASCT).

Study	No. of patients	Induction-CTx	Response after				Median OS (%)
			Induction (%)		ASCT (%)		
			≥nCR	≥VGPR	≥nCR	≥VGPR	
[171]	74	Bortezomib, thalidomide, dex (VTD)	36	60	57	77	NR
	79	Thalidomide, dex (TD)	9	27	28	54	
[165]	102	Lenalidomide, low/high dex + ASCT*					94 at 2 years
	91	Lenalidomide, high dex	4 [†]	52	NR	NR	80 at 2 years
	120	Lenalidomide, low dex	2 [†]	11			91 at 2 years

*Only ASCT, others only induction-CTx.

[†]Without evaluation of bone marrow.

CTx, chemotherapy; nCR, near complete remission; VGPR, very good partial remission; OS, overall survival; NR, not reached.

Efforts to improve the efficacy and applicability of ASCT have prompted a series of randomized trials examining different conditioning strategies. Studies that compared a modified regimen using

total body irradiation (TBI), busulfan, and cyclophosphamide (Bu/Cy) with MEL200 conditioning demonstrated equivalent OS rates but more toxicity with the TBI/Bu/Cy conditioning [57], thus supporting the continued use of MEL200. Similarly, earlier analyses had failed to show any advantages for Bu-conditioning [41] compared to MEL200. Furthermore, TBI added to MEL-conditioning also failed to provide survival advantage compared to MEL200 [58] (EFS 21 months vs. 20.5 months, respectively); however, TBI was associated with more toxicity [59]. Finally, a randomized trial comparing early versus late ASCT demonstrated improved PFS for earlier transplantation (39 months vs. 13 months), while OS was not significantly different. Early ASCT was also associated with an improved quality of life and higher remission rates, thought to arise because of the better performance status of the patients with early ASCT who were also less heavily pretreated [60–70] and thus less likely to have multi-drug resistant disease.

Future studies will need to more clearly define the benefit of ‘upfront’ ASCT versus deferring the procedure, as current data suggest that the median OS with early versus delayed ASCT may be similar, bearing in mind, of course, that with later-scheduled ASCT, patients may never actually get to transplant. Current transplant approaches, as summarized in Table III, utilizing novel induction regimens with single- or tandem-ASCT approaches have resulted in impressive response and OS rates. However, one of the most important prognostic factors for achieving benefit from ASCT remains the ability to achieve CR. Failure to achieve CR or the loss of CR status is independently associated with inferior survival [27,71].

Currently, clinical trials in younger patients (<65 years of age) are exploring the concept of deferring early ASCT in favor of novel agent combinations such as dexamethasone and lenalidomide (Rd) or a triple-agent combination also including bortezomib (VRd). A trial of the GIMEMA study group is currently comparing four cycles of Rd induction followed by either six MPR (melphalan, prednisone, lenalidomide) cycles or tandem-ASCT with MEL200. Preliminary results suggest similar 1-year PFS and OS rates after three cycles of MPR versus MEL200 (96% vs. 94% and 98% vs. 99%, respectively) [38]. While longer follow-up of these trials is awaited, the above recommendations for patients up to the age of 65 years with ASCT remain reasonable. In addition, the durability of the responses and the efficacy of salvage treatment after the use of novel agents are still unknown, whereas these data for ASCT are more mature. Finally, in patients without adverse prognostic factors, the life expectancy with ASCT is still more than 80% at 5 years, with a 30% chance of long-term remission [53].

The issue of one versus two or more transplants

A variety of strategies have been under evaluation to achieve higher CR rates in the first-line therapeutic setting; this includes the use of tandem-ASCT approaches, particularly for patients with insufficient response following an initial ASCT [72]. Studies comparing tandem- versus single-ASCT have demonstrated improved CR rates by 1–15%, significantly prolonged EFS of 5–12 months, and an OS benefit in one analysis [72–74]. However, the benefit of a second ASCT is probably restricted to patients failing to achieve a CR or very good partial response (VGPR) with the first ASCT.

Despite treatment intensification, MM relapse usually occurs after ASCT and allo-SCT [1,3, 16,17], presumably because all patients harbor a proportion of MM cells with an anti-apoptotic phenotype conferring a high level of drug resistance. In this respect, the cell of origin of MM is still unclear, possibly arising in a plasmablast, a PC precursor, or even a more mature PC [2,75]. Moreover, transformation from primarily medullary (BM) to secondary extramedullary (EM) MM can evolve spontaneously or after ASCT [17], and it is theoretically possible that transplant strategies may select for more aggressive MM clones with unfavorable biology. Preliminary reports provide some evidence supporting this hypothesis [17,76].

Maintenance

The growing number of therapeutic options for MM have significantly improved ORR, EFS, and OS for patients with MM; however, the tumor still remains incurable, with disease relapse being inevitable. Consequently, maintenance therapies appear to be a logical strategy for the prolongation of survival and are currently pursued worldwide. The ideal maintenance therapy should improve not only PFS and OS, but also quality of life, and therefore have few side effects and be easy to administer. Until now, only three anti-neoplastic agents— α -interferon (α -IFN), glucocorticoids, and thalidomide—have been adequately studied [77–94]. Maintenance with α -IFN is of only marginal benefit after either standard therapy or ASCT. A number of studies showed a trend toward improved response duration and relapse-free survival [77–81], but others failed to corroborate these findings [82–84], and OS was not prolonged by IFN treatment after standard therapy [77–84]. Furthermore, when administered after ASCT, the value of α -IFN-maintenance is similarly controversial, with only one study showing a PFS and OS benefit [61]. In this respect it is interesting to note that α -IFN seemed to be beneficial only in those patients with the lowest tumor burden and who had achieved at least a CR or VGPR after induction and ASCT [61]. These results and the emergence of alternative therapies that are less toxic, easier to administer, and potentially more effective have led to the abandonment of α -IFN as a maintenance therapy for MM [1,10]. Steroids are perhaps the simplest agents to give for maintenance therapy, but their efficiency has been tested in only a few studies, mostly after standard therapy. Contrary to α -IFN, OS and PFS could be prolonged significantly [94] with 50 mg prednisone on alternate days (so as to reduce the side effects related to chronic steroid exposure), and it was well tolerated [94]. Furthermore, when given with α -IFN, steroids were similarly well tolerated, reproducibly improved PFS [84,85], and in one study also improved OS after standard therapy [85]. Positive effects on ORR were also observed, if applied after ASCT [85]. Although the use of steroids is a promising approach and has found its way into clinical practice due to its easy application, tolerability, and low costs, the paucity of data that are available do not justify their general recommendation, but warrant further studies on benefits, side effects, and quality of life [86,87]. Promising maintenance strategies also include the use of novel agents, such as IMiDs, bortezomib, and others, either alone or in combination with other agents. Since these drugs directly target MM cells and their tumor microenvironment, they may be effective in interrupting cell-adhesion mediated drug resistance, and are potentially of particular use in the setting of a low tumor burden and minimal residual disease [86,87]. Thalidomide has been tested in several studies, mostly after ASCT, and when administered as a single agent, it significantly prolongs PFS, OS, and CR rates [88–91]. Feyler *et al.* showed that the doses used (five dose cohorts [50, 100, 200, 250, 300 mg] of 100 patients) did not influence disease outcome, but greatly affected toxicity. Maintenance doses of >200 mg were largely unachievable, and peripheral neuropathy was the main toxicity, whereas lower doses enabled more patients to stay on the drug for more prolonged periods of time with fewer side effects [89]. As anticipated with the lower doses as currently used (usually 50–200 mg/day), thalidomide was more effective when used for maintenance than for relapse [40,89]. Importantly, in this respect, two subsets of patients do not appear to benefit from thalidomide maintenance, those with 13q14 deletion (del13) and patients achieving a VGPR [40,91], which implies that for patients with del13, alternative strategies need to be developed and that thalidomide should be stopped with the achievement of a VGPR in order to reduce toxicity and the development of drug resistance. However, it should be noted that these studies were not designed or powered to answer questions in relation to the outcome of patient subsets. The incidence of resistance during thalidomide maintenance and its influence on repeated thalidomide usage in subsequent salvage therapy regimens have also been investigated [91,92]. Whereas some earlier trials suggested

unfavorable effects on subsequent salvage therapies after initial thalidomide exposure [85,91], others have found similar responses to the drug on second exposure [15]. Further studies have also shown the efficiency of thalidomide on OS and PFS when combined with steroids and interferon [1,93]. In this regard, thalidomide was well tolerated in a dose of up to 200 mg, if administered alone or with steroids [40,88–91,93], whereas, not surprisingly, tolerability decreased substantially when used in combination with interferon. Neuropathy is the most common side effect, followed by fatigue and constipation [15,40,88–93], while thrombotic events were not statistically increased with thalidomide maintenance [15,40,88–92], suggesting that when given later in the course of the disease following de-bulking of tumor, the thromboembolic risk is much less than at diagnosis. This underlines the importance of the association between tumor mass and thrombosis when thalidomide is administered, and has led to risk-adapted antithrombotic recommendations [95]. In summary, thalidomide is an attractive and effective option for MM disease maintenance approaches and is still being studied in clinical trials.

Similarly, bortezomib and lenalidomide are being evaluated in ongoing clinical trials [96–101]. Preliminary results suggest that bortezomib maintenance may favorably impact on the time to MM recurrence after ASCT, and is being investigated in MM trials in both younger (<60 years) and older patients (e.g. DSMM trials). The use of a therapy regimen that combines bortezomib, thalidomide, and dexamethasone (VTD) as maintenance treatment in 19 patients who had achieved a VGPR or CR demonstrated a reduction of the clonal cell burden as assessed by real time-polymerase chain reaction (RT-PCR); however, in most patients, VTD was unable to completely reduce the tumor load below the sensitivity threshold with PCR-based approaches [102]. Moreover, after initial anti-MM treatment, VTD could perhaps be considered more as a consolidation approach rather than ‘maintenance,’ and may not be well tolerated for prolonged periods of administration.

Novel agents

Thalidomide/dexamethasone (TD) has been compared to VAD as induction before ASCT, demonstrating superior pre-ASCT responses but with no difference in ORR post-ASCT (Table III). In contrast, the Intergroup Francophone du Myelome (IFM) have reported preliminary results from a randomized trial comparing bortezomib/dexamethasone (VD) to VAD pre-ASCT, and with more than 400 patients enrolled they demonstrated significantly superior response rates with VD both before and after ASCT [52]. As bortezomib use does not compromise stem cell mobilization, it is currently under evaluation as a component in a variety of other induction protocols (e.g. cyclophosphamide, dexamethasone, and bortezomib in the DSMM XI trial) [103,104], with a randomized trial of bortezomib, thalidomide, and dexamethasone (VTD) showing superior responses when compared to TD (Table III). Lenalidomide with lower dexamethasone doses (Rd: 160 mg of dexamethasone per 28 day cycle) has been compared to lenalidomide with standard high-dose dexamethasone (RD: 480 mg of dexamethasone per 28 day cycle). Both regimens induced high response rates, but the former schedule resulted in fewer infectious complications than the former and was thus overall better tolerated (Table III) [41,50,105].

While bortezomib, thalidomide, and lenalidomide have already been integrated into anti-MM schedules, there are many other promising therapeutic agents being used in early clinical trials. These include carfilzomib [106–108], pomalidomide [109,110], multikinase inhibitors (MKIs), antiangiogenic approaches, antibodies, arsenic trioxide, farnesyl transferase (FTI)-, histone deacetylase (HDAC)-, heat shock protein-90 (HSP-90)-, and PI-3K/PKD/mTOR-inhibitors, and various other agents which can stabilize relapsed and/or refractory MM. Within this context, clearly the challenge will be to identify subgroups of patients who will benefit most from the different

agents and to incorporate targeted therapies into the management on the basis of an increased understanding of the biology of MM [1,2,75, 111,112].

Allografting in the era of new drugs

Myeloablative allo-SCT has been largely abandoned in MM management because of unacceptably high transplant-related mortality (TRM). In the late 1990s, the introduction of non-myeloablative and reduced intensity conditioning (RIC) regimens, which rely on a putative graft-versus-MM effect, have dramatically reduced TRM to <15%, while achieving CR rates of up to 53–73% and increasing the upper age limit for transplant to 65–70 years [113,114]. Although 30–35% of patients obtain prolonged disease control and may even be cured, relapse and disabling chronic graft-versus-host disease (GVHD), in a subset of patients, remain matters of concern. Fortunately, relapsed disease post-allo-SCT is amenable to salvage therapies, including the use of novel therapies [115], and importantly, preliminary data suggest that the maintenance of a graft-versus-MM effect and the administration of novel agents are not mutually exclusive. Agents such as bortezomib may also contribute to reducing the incidence and severity of GVHD [116]; however, despite these advances, the role and timing of allo-SCT in the era of new drugs still remain to be determined, particularly as recently published outcomes with allo-SCT are from studies initiated before the availability of novel agents.

Initial therapy in elderly patients

In the elderly, the three most commonly used regimens are combinations of melphalan, prednisone, and thalidomide (MPT; grade A recommendation, level Ia evidence); of melphalan, prednisone, and bortezomib (MPV; grade A recommendation, level Ia evidence); and of melphalan, prednisone, and lenalidomide (MPR; grade B recommendation, level IIa evidence).

Several studies have compared MP versus MPT in elderly patients with newly diagnosed MM, all consistently reporting that MPT resulted in higher ORR and longer PFS [15,117–119]. A recent meta-analysis has confirmed the superiority of MPT in terms of response and survival [120]. These results support the use of MPT as one of the standards of care in elderly patients with MM, bearing in mind that neurological adverse events, infections, cardiac toxicity, and thromboembolism are increased with MPT when compared to MP. Antithrombotic prophylaxis is recommended according to risk factors as previously described [95], and the doses of thalidomide need to be adjusted based on tolerance in the elderly so as to minimize toxicity. In patients >75 years of age, the recommended dose is 100 mg/day [118].

MPV resulted in significant improvements in ORR, time to progression, and OS compared to MP; however, the incidence of peripheral neuropathy, gastrointestinal complications, and herpes zoster infection was higher with MPV. When comparing MPV with bortezomib, thalidomide, and prednisone (VTP), there were no differences in ORR, but MPV had less non-hematologic adverse events than VTP. The thalidomide plus MPV (VMPT) regimen induces even higher VGPR and CR rates than MPV, and an ongoing randomized study of VMPT versus VMP suggests an improved 2-year PFS of 70% vs. 58%, but with no difference in 2-year OS rates (89.6% and 89%, respectively), with longer follow-up clearly needed [121]. Finally, preliminary data suggest that with weekly instead of twice-weekly bortezomib infusions, with or without thalidomide combinations, the incidence of grade 3/4 peripheral neuropathy can be reduced without substantially compromising ORR [122,123].

MPR has been tested in a single-arm study of 54 newly diagnosed patients >65 years and induced an ORR of 81%, with a VGPR rate of 47.6%, median time to progression and PFS of 28.5 months, and a 2-year OS of 90.5% [124]. This led to the initiation of a three-arm phase III trial comparing

MPR-R (MPR followed by lenalidomide maintenance) versus MPR versus MP, and an ECOG trial comparing MPR versus MPT. In the former trial, with a median follow-up of 9.4 months, early results show a PFS which has not yet been reached with MPR-R, versus 13 months with MP, and a 1-year OS-rate of 92% [125]. Interestingly, however, the PFS with MPR is the same as with MP (both 13 months), in contrast to the previously reported non-randomized trial of MPR showing a PFS of 28.5 months [124,125].

Treatment of relapsed/refractory disease

IMiD and bortezomib combination schedules as described in Tables II and IV have become part of standard practice, and are continuing to be evaluated in ongoing clinical trials. Combination schedules as depicted in Table IV have demonstrated high levels of activity in relapsed/refractory (RR) MM and now need to be tested in larger patient cohorts, with longer observation periods and optimally compared against each other. An increased range of therapeutic options for RR MM have become available in the past decade, with patients relapsing after the year 2000 demonstrating a 12-month improvement in survival from the time of relapse compared to those who relapsed before this date (23.9 months vs. 11.8 months) [126]. However, in the context of RR MM many questions remain unanswered, the most prominent being whether all active agents should be used at the same time or sequentially, and whether single-, double-, triplet- or four-drug combinations are optimal. Thus, the therapeutic management of RR MM patients depends on various factors, including: prior drug exposure and efficacy, the clinical characteristics of the RR MM, and patient characteristics. A detailed understanding of drug combinations used previously and the degree and duration of response is critical for the decision about what relapse treatment should be used, since—if aggressive relapse occurs—multidrug combinations may be preferable. Relevant patient characteristics include comorbidities, performance status, bone marrow reserve, organ (particularly renal) function, age, and previously experienced or persisting therapy-related toxicities. In young patients relapsing early after ASCT (<1 year), the goal should be to overcome drug resistance, and therefore one would favor a combination of available potentially effective drugs such as bortezomib, lenalidomide, dexamethasone, and cyclophosphamide, or perhaps bortezomib, dexamethasone, thalidomide, cisplatin, adriamycin, cyclophosphamide, and etoposide. If a good response is achieved, the patient could proceed to allo-SCT or maintenance therapy. If the relapse occurs >3 years after ASCT, an option would be to reintroduce the initial treatment or another novel agent combination followed by a second ASCT. In the intermediate situation, with relapse occurring 1–3 years after ASCT, one might favor attempting to rescue the patient with novel agents, but used in a sequential rather than simultaneous manner. In elderly patients, considerations concerning quality of life, travel distance to the hospital, patient's wishes, and the cost of therapy need to be carefully balanced also. At first relapse a logical choice would be to use a new treatment scheme; at second relapse—usually after having received treatment with bortezomib and an IMiD—a clinical trial with experimental agent(s) should be encouraged [1,33,127].

Table IV. Clinical phase II and III studies in relapsed and/or refractory patients.

Study	No. of patients	Phase	CTx	CR rate (%)	Median TTP (months)	Median OS (months)
[172]	44	II	TD	0	4.2	12.6
[85]	77	II	TD	3*	12	NR
[41]	53	II	CTD	5	8.2	66% at 2 years
[173]	60	II	CTD	4	11 [†]	19
[174]	47	II	CVD vs. VD vs. V	31 vs. 5 vs. 0	NA	NA
[175]	50	II	TD + doxo	26	17 [†]	79% at 1 year
[176]	49	II	DVd-T	20	15.5 [†]	39.9
[177]	62	II	VMDT	13	9.3	NR
[178]	37	II	CVP	53	15	24.3
[179]	64	II	RVD	24	NR	NR
[180]	669	III	V vs. D	6 vs. 0.6	6.2 vs. 3.5	80 vs. 66% at 1 year
[181]	646	III	V vs. V + PLD	2 vs. 4	6.5 vs. 9.3	65 vs. 76% at 15 months
[182]	351	III	RD vs. D	16 vs. 3	11.3 vs. 4.7	NR vs. 20.6
[183]	353	III	RD vs. D	14 vs. 0.6	11.1 vs. 4.7	29.6 vs. 20.2

*CR defined by >50% decline in myeloma protein.

[†]Event-free survival.

CTx, chemotherapy; TD, thalidomide plus dexamethasone; CTD, TD plus cyclophosphamide; CVD, VD plus cyclophosphamide; VD, bortezomib plus dexamethasone; V, bortezomib alone; doxo, doxorubicin; DVd-T, pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide; VMDT, bortezomib, melphalan, dexamethasone, and thalidomide; CVP, cyclophosphamide, bortezomib, and prednisone; RVD, VD plus lenalidomide; D, dexamethasone; V + PLD, bortezomib plus pegylated liposomal doxorubicin; RD, lenalidomide plus dexamethasone; CR, complete response; TTP, time to progression; OS, overall survival; NR, not reached; NA, not applicable.

Supportive care for multiple myeloma-induced and/or -associated complications

Bone disease

Despite substantial innovations in the antineoplastic treatment of MM, specific supportive therapies play a key role in patient management and contribute significantly to what should be considered as optimal patient care. Approximately 80% of patients with MM display lytic bone lesions and/or diffuse osteopenia. Bisphosphonates, which substantially inhibit bone destruction and reduce skeletal related events, are recommended for patients with MM with bone disease [128,129], and do not require the use of biochemical markers of bone metabolism to monitor their use [130,131]. In addition, bisphosphonates have a beneficial impact on pain control, particularly with pain due to osteolytic disease [132]. Other advances in the management of MM bone disease include the use of vertebroplasty and kyphoplasty to treat vertebral fractures. Currently, the international standard for bisphosphonate therapy remains intravenous zoledronic acid 4 mg or pamidronate 90 mg every 3–4 weeks in stage II and III disease. Physicians employing bisphosphonates may wish to consult the updated American Society of Clinical Oncology (ASCO) [130] and other available guidelines on the use of bisphosphonates [129]. Serum creatinine should be monitored before each bisphosphonate application, and the dosage must be reduced in patients with preexisting renal insufficiency (estimated glomerular filtration rate [eGFR] 30–60 mL/min/m²). Furthermore, it is mandatory to monitor serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin regularly [130] in the context of bisphosphonate use. Osteonecrosis of the jaw (ONJ) is a rare but potentially serious side effect associated with the usage of bisphosphonates. However, other important risk factors for its occurrence are invasive dental interventions and oral infections prior to bisphosphonate use. Because of this, patients should be advised to undergo a dental examination before bisphosphonate use and to employ appropriate oral hygiene while being treated [133–136]. Additional risk factors for the development of ONJ are the type and duration of exposure to bisphosphonates. Multimodal therapeutic approaches to this problem have used systemic antibiotic therapy, hyperbaric oxygen therapy, laser therapy, topical

use of chemotherapeutic mouth rinses, and discontinuation of bisphosphonates [133], but no accepted standard approach to the treatment of established ONJ has yet been identified. Importantly, however, preventive measures have been shown to reduce the incidence of ONJ by 75% [129]. Zervas *et al.* have suggested that patients receiving zoledronic acid may have a higher risk of ONJ than patients treated with pamidronate [137], but conversely, zoledronic acid is probably more effective in counteracting the development of skeletal complications [138]. Current guidelines suggest that in the presence of stable MM, one should consider stopping bisphosphonates after 2 years of treatment, with a view to re-starting therapy in the context of recurrent MM.

Renal impairment

Renal impairment (RI) early in the natural history of MM is nowadays considered a less frequent problem due to earlier diagnosis and the more effective induction therapies that are available; nevertheless, with substantially longer OS, a significant proportion of patients will develop late disease complications, including RI. Milder degrees of RI are observed in 25–50% [18] of patients, and during disease progression RI develops in at least 20% of patients. Many factors may contribute to RI including dehydration, infections, hypercalcemia, and nephrotoxic drugs. It has also been suggested that RI can be a predictor of poor prognosis since it may reflect a higher MM burden. Furthermore, therapeutic dose reductions may be needed in these cases, and treatment related mortality (TRM) has been shown to be increased in RI-affected patients [18]. Current analyses are evaluating the development of new treatment approaches for patients with RI where prompt disease control is crucial, with new agents, particularly bortezomib, holding great promise for the rapid reversal of RI [139–141].

Hematologic toxicity

Approximately 70% of patients with MM have anemia resulting either from the disease itself or from their anti-MM therapy, and this can be treated with the recombinant hematopoietic growth factor erythropoietin (EPO). Evidence-based guidelines suggest using EPO when the hemoglobin levels fall below 10 g/dL, and for patients with persistent symptomatic anemia. Evidence from clinical trials supports the use of subcutaneous EPO titrated once the hemoglobin concentration reaches 12 g/dL [142]. Prutchi-Sagiv *et al.* claimed that EPO used in the early stages of MM might boost the immune system and therefore induce an anti-MM effect [143], but other trials have suggested that EPO treatment might have deleterious effects on tumor response and survival, thus tempering the enthusiasm for its use [11,33,144]. Well-known EPO-induced side effects, particularly the increased risk of thrombosis, need to be taken into consideration, especially when used in conjunction with IMiDs [11,33,144].

Infection






Infection is the single most dangerous complication for patients with MM, since disease and therapy impair both cell-mediated and humoral immunity. Patients with MM show an increased susceptibility to viruses, bacteria, mycobacteria, fungi, and other pathogens, and therefore require thorough infection monitoring and appropriate use of prophylactic antibiotics. In addition, all patients after allo-SCT should receive vaccinations for diphtheria, tetanus, hemophilus, influenza viruses including H1N1, poliovirus, measles, mumps, rubella, and *Streptococcus pneumoniae*, whilst for patients with ASCT, vaccinations against influenza and *Streptococcus pneumoniae* are recommended [33,145–148].

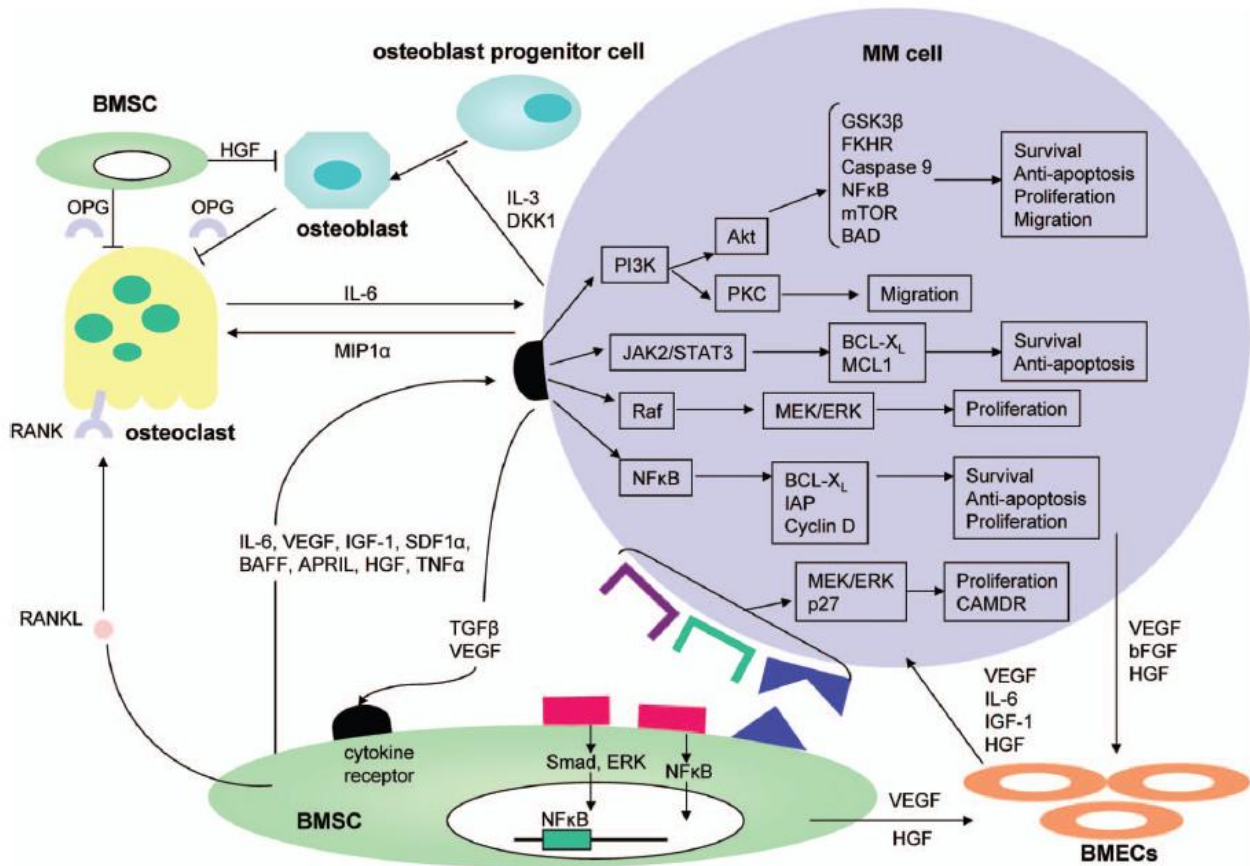
Conclusions and perspectives toward the road to cure MM

Modern treatment approaches provide safe and highly effective therapy, and a substantial proportion of younger patients with MM survive for more than 10 years [1,10,126,149]. Although residual disease may be detectable with molecular methods, current therapy aims at achieving a normal life for patients with MM, with minimization of disease-related symptoms or complications. The most promising therapeutic approach in younger (<65 years) patients is the combination of

transplant procedures (ASCT±RIC allo-SCT) and targeted therapies. In elderly patients (>65 years), MPT or MPV can be considered the standard of care, while dose-reduced tandem-ASCT (MEL140) with novel induction therapies (e.g. lenalidomide/low-dose dexamethasone, Rd) are currently being tested against standard regimens (e.g. DSMM XIII trial), and results are awaited with anticipation.

An increased understanding of the pathobiology of MM has translated into a broadened spectrum of available targeted therapies (Figure 2), which may result in further improvement in patient outcome and quality of life. The discovery of microRNA (miRNA) genes, encoding for a class of small non-coding RNAs acting as negative regulators of gene expression, has added a further level of complexity to our concept of MM cancer biology. It has been reported that the combination of non-random chromosomal abnormalities and other types of genetic alterations or epigenetic events contribute to downregulation or overexpression of miRNAs, which may consequently affect the cell cycle, cell survival, and cellular differentiation programs [150]. MM represents an ideal model for miRNA investigation, since it is associated with recurrent deletions or gains/amplifications that may affect the normal miRNA role. Significant data concerning miRNA in MM have been reported only recently by various groups, showing signatures associated with specific molecular types and suggesting that distinct miRNAs may play an important role in neoplastic transformation and disease progression [151–154]. Experimental data have also recently suggested that miRNA-15a and miRNA-16, which are located in the 13q14 region, frequently deleted in MM, may play a role in MM cell proliferation, representing promising targets for novel therapies [155].

Figure 2. Myeloma network of interacting factors between myeloma cells and cells from the microenvironment (figure modified with kind permission according to illustrations of Hideshima *et al.*, 2002 [186], Hideshima *et al.*, 2007 [187], and Harousseau, 2009 [185]). The diagram shows the interplay between myeloma, microenvironment, chemo-, cytokines, and signaling molecules involved in the pathophysiology of MM and various treatment options that mediate their action through direct cytotoxicity, apoptosis induction, anti-angiogenesis, and/or immunostimulation. MM, multiple myeloma; CAMDR, cell adhesion-mediated drug-resistance; BMSC, bone marrow stromal cell; BMECs, bone marrow endothelial cells; HGF, hepatocyte growth factor; OPG, osteoprotegerin; IL-6, interleukin 6; NFκB, nuclear factor κB; RANK, receptor activator of NFκB; RANKL, receptor activator of NFκB ligand; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; IGF-1, insulin like growth factor-1; SDF-1α, stromal-cell-derived-factor-α; TGFβ, transforming growth factor β; ICAM-1, intercellular adhesion molecule 1 ; VCAM-1, vascular adhesion molecule 1 ; PI3K, phosphatidylinositol 3-kinase; MIP-1α, macrophage inflammatory protein 1α; LFA-1, lymphocyte function antigen 1 ; MUC-1, mucin protein 1 ; VLA-4, very late antigen 4 ; DKK1, Dickkopf 1; MIP1α, macrophage inflammatory protein 1α; TNFα, tumor necrosis factor α.



Novel prognostic tools are also being extensively explored, and cyclins functioning as cell cycle regulators have proved to be of interest, since overexpression of the cyclin genes CCND1, 2, and 3 are recurring abnormalities in human cancer. Recent studies have demonstrated a positive association between CCND1 overexpression and survival in breast cancer and MM. Paradoxically, high cyclin D expression should enhance proliferation and sensitivity to chemotherapy, but MM is characterized by a very low proliferative index [2,156] and drug resistance. However, another explanation for the association between high cyclin D levels and better prognosis could be the binding of the anti-apoptotic transcription factor signal transducer and activator of transcription 3 (STAT3) to CCND1, as described in breast cancer [157]. CCND1 represses STAT3 transcriptional activity, thereby inducing apoptosis and causing less aggressive tumor growth. As the CCND1 protein has a short half-life due to post-translational regulation by ubiquitination and proteasomal degradation, this might provide a therapeutic rationale for blocking CCND1 degradation using a 26S proteasome inhibitor, and consequently amplifying anti-tumorigenic activity [158,159]. Together with *in vitro* and *vivo* analyses, these new basic discoveries relating to gene regulation in tumorigenesis are likely to lead to the development of new treatment options as well as a better understanding of MM pathobiology, and will hopefully further improve the development of future MM treatment [112,160].

Two studies in particular have shown that advances in MM care and treatment do translate into improved survival. Brenner *et al.* demonstrated that between 1990–1992 and 2002–2004, the 5-year OS for MM has increased from 28.8 to 34.7%. The most significant change occurred in younger patients (<50 years), with 5- and 10-year OS rates of 56.7% and 41.3%, respectively [161]. In a second study, Kumar *et al.* demonstrated that patients who relapsed after SCT and were treated with novel agents had a significantly improved median OS of 30.9 months, compared to only 14.8 months for patients not receiving novel agents. Importantly, they also showed that the OS of patients with newly diagnosed MM has improved by 50% over the past decade, albeit in a tertiary referral center [126]. Despite these impressive advances in MM therapy, there are still important

challenges to overcome in the future [1,3,10,11,162]. In addition to targeted therapies, chemotherapeutic regimens with increased antineoplastic efficiency are still needed, since the major cause of relapse after ASCT is the resistance of MM cells to currently available cytotoxic agents.

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